(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
25 October 2001 (25.10.2001)

PCT

(10) International Publication Number
WO 01/78805 A1

(51) International Patent Classification[7]: A61M 1/16, 1/34, B01D 69/02, 69/08, 61/14

(21) International Application Number: PCT/US01/40494

(22) International Filing Date: 11 April 2001 (11.04.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
09/549,131 13 April 2000 (13.04.2000) US

(71) Applicant: TRANSVIVO, INC. [US/US]; Suite 108, 1100 Lincoln Avenue, Napa, CA 94558 (US).

(72) Inventors: GORSUCH, Reynolds; 1119 State Lane, Yountville, CA 94599 (US). GRAGE, Henry; 175 Tenby Terrace, Danville, CA 94506 (US).

(74) Agent: ARNO, Thomas, R.; Knobbe, Martens, Olson & Bear, LLP, 16th Floor, 620 Newport Center Drive, Newport Beach, CA 92660 (US).

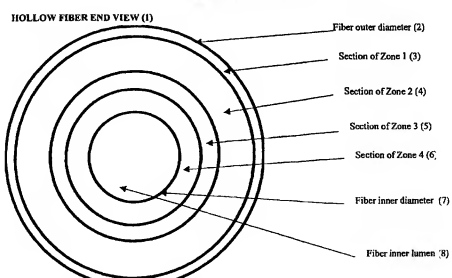
(81) Designated States *(national)*: AE, AG AL, AM, AT, AT (utility model), AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, CZ (utility model), DE, DE (utility model), DK, DK (utility model), DM, DZ, EE, EE (utility model), ES, FI, FI (utility model), GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK (utility model), SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

[Continued on next page]

(54) Title: SPECIALIZED HOLLOW FIBER MEMBRANES FOR IN-VIVO PLASMAPHERESIS AND ULTRAFILTRATION



(57) Abstract: An *in-vivo* plasmapheresis and/or *in-vivo* ultrafiltration membrane comprises a plurality of elongated hollow fibers each fiber having an interior lumen extending along the fiber length, the fiber wall having a plurality of zones between the inner and outer wall surfaces, each of the zones having a mass density different than the mass density of an adjacent zone. The fiber wall is characterized by having a lower mass density zone at the inner wall surface and a higher mass density zone at the outer wall surface.

WO 01/78805 A1

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

SPECIALIZED HOLLOW FIBER MEMBRANES FOR IN-VIVO PLASMAPHERESIS AND ULTRAFILTRATION

Background of the Invention

In U.S. Patent Nos. 4,950,224, 5,152,743, 5,151,082, 5,735,809 and 5,980,478 there are disclosed methods and apparatus for carrying out *in-vivo* plasmapheresis for separating plasma from other blood components within the body and blood vessels of the patient. The apparatus uses pumping means to create a trans-membrane pressure (TMP) and motivate the flow of fluid from within the *in-vivo* system, whereby blood plasma is pumped from the patient to a treatment means such as a dialyzer apparatus in which toxic metabolic waste in the plasma is removed. After the plasma is treated for removal of waste products, excess fluids, toxins, and/or other deleterious plasma proteins, the treated plasma is returned and reintroduced to the patients' blood stream. Such methods are referred to as plasma dialysis, ultrafiltration or blood purification.

These methods of toxin removal from blood as taught by the above patents are unique and substantially superior from conventional means of hemodialysis as presently practiced for both acute and chronic kidney failure, primarily because removal of whole blood from the patient's vasculature is eliminated from the procedure using plasma, or portions of the plasma instead. In conventional hemodialysis procedures hollow fiber membranes are used in the *ex-vivo* dialysis and hemofilter cartridges for blood purification. The blood is routed from the body through the center lumen of the hollow fibers in the cartridges and dialysate fluid is routed over the outside walls of the fibers within the cartridge cavity in counter-flow direction to blood flow. Thus, toxin diffusion and ultrafiltration are from inside the fiber lumen to a compartment outside the fiber walls where the ultrafiltrate and toxin-saturated dialysate are collected for further processing and/or disposal.

Conventional hollow fiber membranes commercially used for present hemodialysis, hemo-ultrafiltration, and dialyzer cartridges fabricated from proprietary and non-proprietary polymer compositions generally utilize two types of morphologies: symmetrical and asymmetrical. In a symmetrical composition, the basic morphology or cellular structure and porosity of the fiber wall is uniform from the inner lumen to the outside surface. In asymmetrical compositions, both morphology and pore structures vary from the inner lumen to the outer surface to meet the high pressure requirements of the filter cartridges in which the TMP inside the fiber lumen is high (100 - 310 mmHg) while the blood flow itself in the fibers is near stagnant (2 - 300 ml/min/7,000 fibers = .042 ml/m/fiber). These commercial membranes generally also have poor structural strength, acceptable in an encapsulated device external to the body but which would not be acceptable for an *in-vivo* placement for safety reasons. Such conventional fiber membranes are not suitable for the demanding environment of the *in-vivo*, high blood flow (vena cava = 2.5 l/min), low TMP ($\leq$ 50 mmHg), and unencapsulated environment of plasma extraction devices described by the aforesaid patent applications.

Summary of the Invention

The present invention is directed to specialized hollow fiber membranes having the function of separation of plasma or a portion of the plasma from blood and having the unique morphology, performance properties and materials

biocompatible characteristics necessary for effective and optimal utilization for *in-vivo* vascular implantation as the operating element in catheter-based devices as described in the aforesaid patents and other such similar devices for the separation and extraction of plasma and plasma components from the blood. The ultrafiltrate (exudate) may be transported *ex-vivo* via a catheter lumen where it is discarded, or treated by cascade filtration means, dialysis (solute diffusion) means, or other methods known to the art, and returned to the patient via a separate lumen in the catheter.

The hollow fiber membrane of the invention is tubular in shape and generally circular in cross-section, having a coaxial inner lumen along the length of the fiber in its center. The wall volume of the fibers is asymmetrical with a variable morphology from the outer diameter to that of the inner diameter, having a higher mass density at the outer wall and a lower mass density at the inner wall. The fibers are designed to facilitate ultrafiltration with the permeate outside the fibers and the exudate inside the fibers. The inner lumen of all fibers in a fiber extraction assembly are in direct fluid communication with the access lumen of the catheter which provides means for transporting the exudate *ex-vivo*.

Brief Description of the Drawings

Figure 1 is a schematic end view of a hollow fiber illustrating the membrane morphology structure having four zones;

Figure 2 is a scanning electron microscopy (SEM) image of a cross-section of a portion of the fiber of the invention at 400 μm magnification showing four zones of the asymmetrical wall structure between the inner and outer fiber wall surfaces;

Figure 3 shows a portion of a cross-section of a portion of the fiber at a magnification of 5,000 μm;

Figure 4 is a SEM cross-section of Zones 1, 2 and 3 of the fiber shown in Figure 2 at a magnification of 1,000 μm;

Figure 5 is a SEM cross-section of Zones 3 and 4 of the fiber shown in Figure 2 at a magnification of 1,000 μm;

Figure 6 shows a transverse view of the inner lumen wall of the fiber at a magnification of 5 000 μm; and

Figure 7 is a graph illustrating the hollow fiber membrane sieving coefficient curves.

Detailed Description of the Preferred Embodiment

As illustrated in Figures 1-5, the features of the fiber wall of the membrane of the invention include a pore and void structure defined within frames or solid walls which form boundaries of the pores. The pores are voids of variable definitive sizes which permit passage of fluid through the fiber wall to the lumen and which pores obstruct the passage of components larger than the pore diameter. As illustrated particularly in Figure 3, the pores are irregular-shaped voids bounded by solid frames to form irregular tortuous paths for irregular and regular-shaped solutes. The wall structure of the fiber from the outer surface to the lumen is a continuum with non-linear pore and void distribution. The resulting structure is a continuous change in mass density between the outer surface of the fiber

and the inner lumen surface. Thus, it is convenient to describe these changes in mass density es sections of the wall area heving an average nominal pore size, porosity and wall mass in terms of zones with macro-functi ns.

In Figure 1, the wall structure illustrated has four zone sections, each zone characterized by a different mass pore density based on the average nominal pore size in the respective zones. The section of Zone 1 i: adjacent to the fiber outer surface or outer diameter. Zone 1 forms the fiber interface with the permeate blood fl nw and although being the thinnest zone contains the highest density of operationally controlling pores for the fiber membrane performance. Thus, Zone 1 has the principal effect in the filtration process for controlling the trar s-membrane flux (TMF) which is dependent on pore size, porosity and virtual membrane thickness.

The section of Zone 2, while having some flux-controlling pores, is principally a struct ral member for providing strength to the fiber as well as acting as a conduit for exudate flow to the section of Zone 3. The latter is principally a structural member with expanded pores for reducing the hydraulic resistance and providi g a fluid conduit to the lumen of the fiber, and thus, in the example, as shown, has little filtration function. The secti n of Zone 4 has very large voids and pores with very little solid structure, thereby having the primary function of a m jor reduction of hydraulic resistance through the membrane and defining the fiber inner lumen diameter surface.

Figure 2 illustrates a cross-section of the fiber wall showing the structure of Zones 1-4 at 400 μm magnification. The fiber wall morphology demonstrates the continuum of expanding plurosity and o en spaces from the virtual control pore size of Zone 1 adjacent to the outer fiber diameter to the very open and lo v-flow resistant structure in Zone 4 adjacent to the inner lumen wall.

Figure 3, a cross-section of Zone 1 at a magnification of 5,000 μm, shows pores and the r boundary solid wall frames and the high uniformity of pore geometry end diverse irregular shapes of the individual po e dimensions. It is this high uniformity of pore size and high porosity as well es the thinness of Zone 1 which pi oduces the high separation efficiency and high TMF of the membrane.

Figure 4 shows a cross-section of Zones 1, 2 and 3 at a magnification of 1,000 μm to illustrate the transition of the high-density structure of Zone 1 in comparison to the more open densities of Zones 2 and 3, as well as the uniformity and continuity of fiber structure producing high tensile and elongation strength.

Figure 5, also at a magnification of 1,000 μm, shows the structure of Zones 3 and 4 to illu trate the rapidly expanding open spaces and fluid communication channels which produce the lowered hydraulic resis ance to flow of the exudate and results in a very high TMF as a function of a very low TMP.

Figure 6 is a 5,000 μm magnification of a transverse view of the inner lumen wall showing the highly open but contiguous nature of the structure at that site, facilitating fluid communication of the exudat from the flow through the fiber to the fiber lumen.

Figure 7 illustrates a sieving coefficient curve to provide a measure of membrane performa ce *in-situ* in an operating environment. The sieving coefficient curves illustrated are determined or generated by measuring the amount of a series of specific solutes or proteins in exudate passed through the membrane by convection as a percentage of the amount of the permeate of the same solute or protein in the blood. The vertical a is of the chart

illustrated is linear from 0 to 100% and the horizontal axis is semi-logarithmic in two scales; the first scale is expressed in pore size in μm; the second scale is expressed in the molecular weight of the solute in Daltons. Curve 10 of Figure 7 represents the typical curve of a plasma extraction membrane with exudate performance in Areas A and B. Curve 11 shows the typical exudate performance of a hemofilter (ultrafiltration) membrane with exudate performance in Area B, wherein Areas A plus B plus C constitute all components of the blood. Thus, Curve 10 represents the typical sieving coefficient curve for membranes with pores in the 0.3 to 0.7 μm diameter size, as used in plasmepheresis while Curve 11 represents a typical sieving coefficient curve for membranes with pores in the 0.006 to 0.009 μm diameter size used for ultrafiltration.

The driving force for convective transport of the plasma fluid and solutes is the TMF equal to P_f x TMP (and linear below the critical flow limit) where P_f is the hydraulic permeability of the membrane, and:

$P_f = (n \pi r_p^4) / (\tau \mu \Delta x)$ Where:

(n) = Porosity (number of pores/unit area)

(π) = 3.14159

(r_p) = Pore radius (pore size)

(τ) = Tortuosity of path

(μ) = Viscosity of solution

(Δx) = *Membrane thickness*

It should be noted that the largest leverage to obtaining optimum TMF is the radius of the pores because it is raised to the fourth power. The next largest lever is the porosity or number of such pores/unit area and the effect of the pore radius which is multiplied by the porosity. Functional optimization for this application therefore also relies on achieving a tight standard deviation of pore radius in the effective zone of filtration as well as a high density of such pores in the primary filtration zone of the membrane. The relationship is also affected by temperature to the extent that temperature changes the value of the parameters including the viscosity of the solution.

The membranes of the present invention may be prepared using any suitable polymer fibers which will result in a hollow fiber membrane which meets the biocompatibility requirements and properties of the invention. Such membrane materials and surfaces must be highly biocompatible and resist clotting, protein adhesion and detrimental interaction with immune system components. The structural strength of the hollow fiber membranes must be high enough to safely withstand implantation as well as the hydraulic and physical perturbations existing in the vena cava environment. Thus, the functional convection extraction efficiency of such hollow fibers must be suitable to meet clinical treatment requirements in the smallest possible size in order to fit within the vena cava without stress. The membranes also must be designed with a morphology optimized for blood flow on the outside of the fiber and ultrafiltrate on the inner lumen of the fiber. A number of potentially suitable polymer fiber membrane materials are described in the aforesaid patents including fibers produced from polyurethane, polypropylene, polyethersulfone, polycarbonate, nylon, polyimide and other synthetic resins known to those skilled in the art. A preferred polymer is polysulfone membrane, and more preferably a polysulfone modified with a polyethylene oxide-polyethylene glycol

copolymer. Such polysulfone fibers are produced in the presence of polymer dopes, core fluids, and coagulation fluids using processes including membrane spinning methods which achieve the desired product. Examples of such additive materials used in the polymerization process, spinning process and/or fiber membrane production include polyvinyl pyrrolidone, N-methyl pyrrolidone, dimethyl acetomide, dimethyl sulfoxide, and mixtures of two or more such materials. Such polysulfone fibers have been found to have the least detrimental characteristics that influence protein membrane interaction such as crystallinity, ionic groups, hydrogen bonding groups and hydrophobic sites. The specific method used for producing the aforesaid polymers as well as the processes and parameters during the manufacture are known to those skilled in the art. The general specifications and variation range of parameters for the hollow fiber membranes for medical applications within the scope of the present invention are as follows:

PLASMAPHERESIS APPLICATIONS

PARAMETER	SPECIFICATIONS		RANGE OF APPLICATION	
	FROM	TO	FROM	TO
Outer Diameter μm	735	765	200	800
Inner Diameter μm	240	260	50	700
Wall Thickness μm	175	260	50	600
Zone 1 mean flow pore diameter μm	0.7	0.8	0.3	1
Zone 4 pores @ ID diameter μm	5	40	1	60
Tensile force @ Break Pounds/in^2	750	900	500	1500
Elongation @ Break %	65	80	50	150
Fluid Flux (H_2O) ml/min/cm^2 @ 100 mmHg	1.0	1.5	1.0	10
TMF plasma ml/min/cm^2/10 mmHg	.75	4	.5	9

ULTRAFILTRATION APPLICATIONS

PARAMETER	SPECIFICATIONS		RANGE OF APPLICATION	
	FROM	TO	FROM	TO
Outer Diameter μm	450	650	123	750
Inner Diameter μm	250	325	100	700
Wall Thickness μm	150	200	40	400
Zone 1 mean flow pore diameter μm	0.01	0.03	0.005	0.05
Zone 4 pores @ ID diameter μm	5	40	1	60
TMF H_2O ml/min/cm^2/10 mmHg	.75	4	.5	9
Tensile force @ Break Pounds/in^2	700	800	450	1200
Elongation @ Break %	50	65	40	100

Examples of medical applications for which the hollow fiber membranes of the present invention may be used include the following: therapeutic apheresis applications including plasma exchange, cascade protein separation by filtration, cascade protein removal or modification by adsorption cartridge, cryogenic modification, or chemical adaptation; fluid management application or congestive heart failure both acute and chronic; tissue engineering

applications including online generation of media for bioreactor from xenogenic, allogenic, and autogenic sources; continuous renal replacement therapy (CRRT) for both acute and chronic kidney failure; edema prevention therapies for MODS (multiple organ dysfunction syndrome); cytokine removal or modification in therapy for septic shock or SIRS (systemic inflammatory response syndrome); plasma extraction from peritoneal ascites; intermittent hemodialysis (IHD) or hemodiafiltration; and ARDS (acute respiratory distress syndrome) therapy by reduction of pulmonary edema and physiological pulmonary dead space.

Additional uses for the specific membranes of the present invention as well as those covered in the aforesaid U.S. patents will be evident to those skilled in the art.

WHAT IS CLAIMED IS:

1. An *in-vivo* plasmapheresis or *in-vivo* ultrafiltration membrane comprising a plurality of elongated hollow fibers each fiber having an interior lumen extending along the length thereof and defined by an inner wall surface, wherein the morphology of said fiber wall is asymmetrical between said inner wall surface and the fiber outer wall surface, said fiber wall characterized by having a higher mass density adjacent to the outer wall surface and a lower mass density adjacent to said inner wall surface.

2. A membrane of Claim 1 wherein the higher mass density fiber wall is characterized by pores having a smaller average nominal pore size as compared to the average nominal pore size in the lower mass density fiber wall.

3. A membrane of Claim 1 further characterized by the fiber wall having a plurality of zones between the inner and outer wall surfaces, each of said zones having a mass density different than the mass density of an adjacent zone, said fiber wall characterized by having a lower mass density zone at the inner wall surface and a higher mass density zone at the outer wall surface.

4. A membrane of Claim 3 wherein said membrane fiber wall has two mass density zones.

5. A membrane of Claim 3 wherein said membrane fiber wall has three mass density zones.

6. A membrane of Claim 3 wherein membrane fiber wall has four or more mass density zones.

7. A membrene of Claim 3, 4, 5, or 6 wherein each of said zones is characterized by a different average nominal pore size.

8. A membrane of Claim 7 capable of *in-vivo* plasmapheresis wherein said lower mass density zone is characterized by a nominal average pore diameter of between about 1 μm and about 60 μm.

9. A membrane of Claim 7 wherein said higher mass density zone is characterized by a nominal average pore diameter of between about 0.3 μm and about 1 μm.

10. A membrane of Claim 8 wherein said higher mass density zone is characterized by a nominal average pore diameter of between about 0.3 μm and about 1 μm.

11. A membrane of Claim 1 or 3 characterized by having the capability of extracting at least 0.75 ml/min/cm^2/mm Hg of blood plasma at trans-membrane pressures of between about 5 and about 20 mm Hg.

12. A membrane of Claim 7 capable of *in-vivo* ultrafiltration wherein said higher mass density zone is characterized by a nominal average pore diameter of between about 0.005 μm and about 0.05 μm.

13. A membrane of Claim 1 or 3 comprising a polysulfone fiber.

14. A membrane of Claim 13 wherein said polysulfone includes a copolymer of polyethylene oxide and polyethylene glycol.

15. A membrane of Claim 13 wherein said polysulfone fiber is produced in the presence of a composition comprising polyvinyl pyrrolidone, N-methyl pyrrolidone, dimethyl acetomide or dimethyl sulfoxide, or mixtures of two or more thereof.

16. A membrane of Claim 15 wherein said polysulfone includes a copolymer of polyethylene oxide and polyethylene glycol.

17. A plasmapheresis or ultrafiltration assembly compressing a membrane of Claim 1 or 3 and a catheter in direct fluid communication with said interior lumen of said fiber.

18. A plasmapheresis or ultrafiltration assembly of Claim 17 comprising a dual lumen catheter.

19. A plasmapheresis membrane of Claim 8 or 10 having a plasma trans-membrane flux of between about 0.5 and about 9 ml/min/cm^2 @ 10 mm Hg.

20. A plasmapheresis membrane of Claim 1 or 3 wherein said higher mass density is characterized by a nominal average pore diameter of between about 0.7 μm and about 0.8 μm.

21. A plasmapheresis membrane of Claim 20 wherein said lower mass density is characterized by a nominal average pore diameter of between about 5 μm and about 40 μm.

22. A plasmapheresis membrane of Claim 21 having a plasma trans-membrane flux of between about 0.75 and about 4 ml/min/cm^2/@10 mm Hg.

23. An ultrafiltration membrane of Claim 1 or 3 wherein said higher mass density is characterized by a nominal average pore diameter of between about 0.01 μm and about 0.03 μm.

24. An ultrafiltration membrane of Claim 23 wherein said lower mass density is characterized by a nominal average pore diameter of between about 5 μm and about 40 μm.

25. An ultrafiltration membrane of Claim 24 having a trans-membrane flux (H_2O) of between about 0.75 and about 4 ml/min/cm^2/@10 mm Hg.

26. A method of carrying out *in-vivo* plasmapheresis and/or *in-vivo* ultrafiltretion of a patient's blood, comprising:

implanting a filter device of Claim 1 or 3 within a blood vessel of a patient, and passing blood plasma and toxins through said fiber wall to said interior lumen and directing said blood plasma and toxins from the patient through said interior lumen.

FIGURE 1 MEMBRANE MORPHOLOGY STRUCTURE

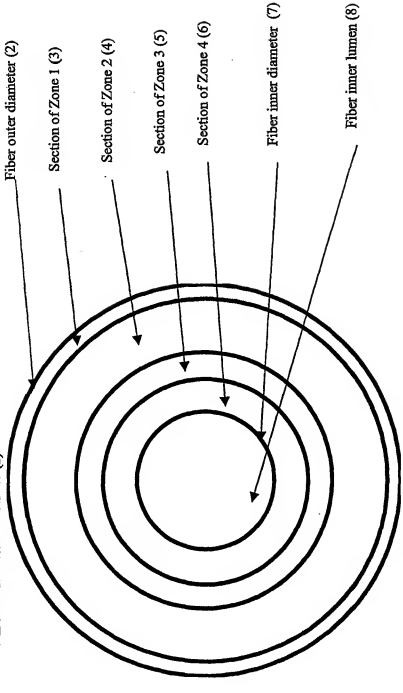


FIGURE 2

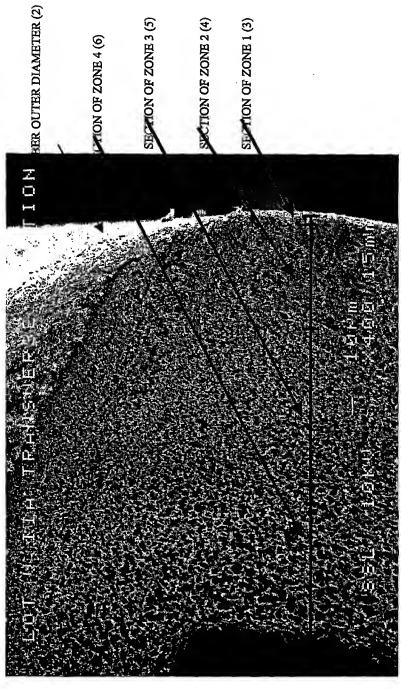

ER OUTER DIAMETER (2)
ON OF ZONE 4 (6)
SECTION OF ZONE 3 (5)
SECTION OF ZONE 2 (4)
SECTION OF ZONE 1 (3)
IBER INNER IAMETER (7)

FIGURE 3

SEM OF SECTION ZONE 1 PORE STRUCTURE (3)

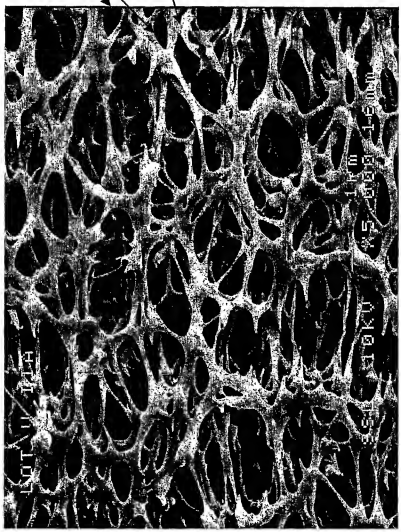


FIGURE 4

SEM OF FIBER CROSSECTION SECTION ZONES 1,2 AND 3

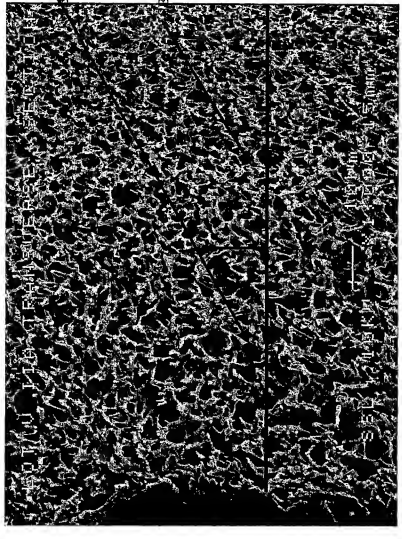
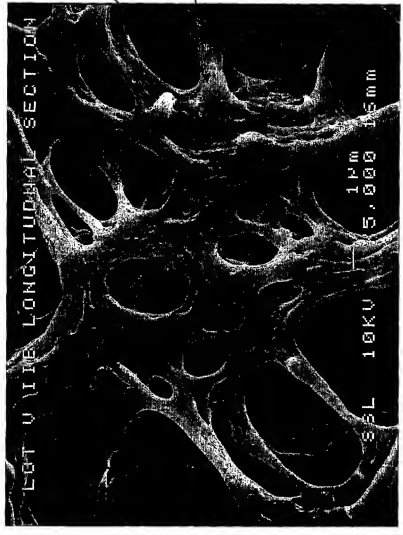


FIGURE 5

SEM OF CROSSECTIONS ZONES 3 AND 4

FIGURE 6


LOT U VINE LONGITUDINAL SECTION
SEL 10KV 5,000 1MM
PORES
PORE WALL SOLIDS

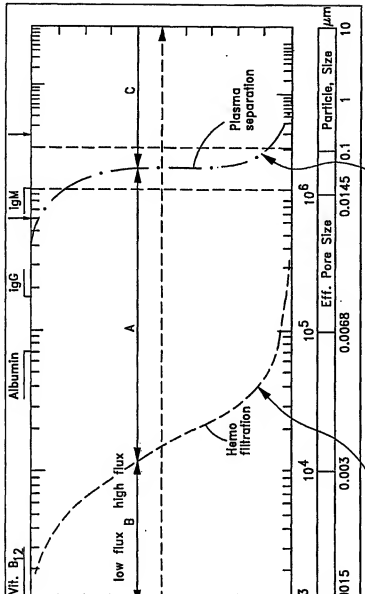

SIEVING COEFFICIENT
S
1
0.5
0
Vit. B12
Albumin
IgG
IgM
low flux
B
high flux
A
C
Hemo filtration
Plasma separation
10^3
10^4
10^5
10^6
Eff. Pore Size
0.0015
0.003
0.0068
0.0145
Particle, Size
0.1
1
10
μm
(11)TYPICAL SIEVING COEFFICIENT CURVE FOR MEMBRANES WITH PORES IN THE .006 TO .009 μm DIAMETER SIZE FOR
(10)TYPICAL SIEVING COEFFICIENT CURVE FOR MEMBRANES WITH PORES IN THE .3 TO .7 μm DIAMETER SIZE FOR

FIG. 7

INTERNATIONAL SEARCH REPORT

Inter ıal Application No
PCT/US 01/40494

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61M1/16 A61M1/34 B01D69/02 B01D69/08 B01D61/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61M B01D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

WPI Data, PAJ, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 882 494 A (ASAHI KASEI KOGYO KK) 9 December 1998 (1998-12-09) claims 1-3; examples ---	1-4, 7-10,13
X	FR 2 566 003 A (INSTITUT NATIONAL DE RECHERCHE CHIMIQUE APPLIQUEE) 20 December 1985 (1985-12-20) claims; example 3 ---	1-10,13
X	DATABASE WPI Week 199809 Derwent Publications Ltd., London, GB; AN 1998-094881 XP002176162 & JP 09 323031 A ((ASAH) ASAHI MEDICAL CO LTD), 16 December 1997 (1997-12-16) abstract --- -/--	13-15

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
29 August 2001	10/09/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Cordero Alvarez, M

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inter al Application No
PCT/US 01/40494

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 224 926 A (R.G.F.GORSUCH ET AL) 6 July 1993 (1993-07-06) column 2, line 8-24; claims 1,9,10,13	1,9-11, 17-20
A	US 5 980 478 A (R.G.GORSUCH ET AL) 9 November 1999 (1999-11-09) cited in the application claims 1-19	26
A	US 5 152 743 A (R.G.GORSUCH ET AL) 6 October 1992 (1992-10-06) cited in the application claims 1,3-5,7	9,10 20

INTERNATIONAL SEARCH REPORT

Interi al Application No
PCT/US 01/40494

Patent document cited in search report		Publication date	Patent family member(s)		Publicatio date
EP 882494	A	09-12-1998	US	6165363 A	26-12-2000
			WO	9722405 A	26-06-1997
FR 2566003	A	20-12-1985	AT	68991 T	15-11-1991
			DE	3584562 A	05-12-1991
			DE	3584562 D	05-12-1991
			EP	0183757 A	11-06-1986
			WO	8600028 A	03-01-1986
			US	4882223 A	21-11-1989
JP 9323031	A	16-12-1997	NONE		
US 5224926	A	06-07-1993	US	4950224 A	21-08-1990
			US	5242382 A	07-09-1993
			US	5151082 A	29-09-1992
			US	5152743 A	06-10-1992
			AT	136472 T	15-04-1996
			DE	68926197 D	15-05-1996
			DE	68926197 T	21-11-1996
			EP	0354061 A	07-02-1990
			ES	2088390 T	16-08-1996
			GR	3020503 T	31-10-1996
US 5980478	A	09-11-1999	AU	1075899 A	03-05-1999
			CN	1275087 T	29-11-2000
			EP	1027095 A	16-08-2000
			WO	9919007 A	22-04-1999
US 5152743	A	06-10-1992	US	4950224 A	21-08-1990
			US	5224926 A	06-07-1993
			AT	136472 T	15-04-1996
			DE	68926197 D	15-05-1996
			DE	68926197 T	21-11-1996
			EP	0354061 A	07-02-1990
			ES	2088390 T	16-08-1996
			GR	3020503 T	31-10-1996
			US	5242382 A	07-09-1993
			US	5151082 A	29-09-1992